PATENT COOPERATION TRI TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44*bis*.3(c) and 72.2)

To:

SHIMIZU, Hatsushi
Kantetsu Tsukuba Bldg. 6F
1-1-1, Oroshi-machi
Tsuchiura-shi, Ibaraki 3000847
JAPON

Date of mailing *(day/month/year)* 18 January 2007 (18.01.2007)	
Applicant's or agent's file reference D3-A0405P	**IMPORTANT NOTIFICATION**
International application No. PCT/JP2005/005144	International filing date *(day/month/year)* 22 March 2005 (22.03.2005)
Applicant DNAVEC RESEARCH INC. et al	

1. **Transmittal of the translation to the applicant.**

☐ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).

☑ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. **Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

EP, KR

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yoshiko Kuwahara
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 82 70

TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
D3-A0405P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/005144	22.03.2005	23.03.2004

International Patent Classification (IPC) or national classification and IPC

C12N15/09, A61K35/28, A61K38/00, A61K48/00, A61P1/16, A61P29/00, A61P35/00, A61P37/02, C12N5/10

Applicant

DNAVEC RESEARCH INC.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2005/005144

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2005/005144

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6-7, 20-24, 27-31	YES
	Claims	1-5, 8-19, 25-26	NO
Inventive step (IS)	Claims	22, 28	YES
	Claims	1-21, 23-27, 29-31	NO
Industrial applicability (IA)	Claims	1-31	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: Feldman, E. et al., "Adenovirus mediated alpha interferon (IFN-Alpha) gene transfer into CD34+ cells and CML mononuclear cells", Stem Cells (1997), Vol. 15, No. 5, pages 386 to 395

Document 2: JP 09-501837 A (Rhone-Poulenc Rorer SA), 25 February 1997, entire document

Document 3: Studeny, M. et al., "Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors", Cancer Research (2002), Vol. 62, No. 13, pages 3603 to 3608

Document 4: Duan, H.F. et al., "Treatment of myocardial ischemia with bone marrow-derived mesenchymal stem cells overexpressing hepatocyte growth factor", Mol. Ther. (2003), Vol. 8, pages 467 to 474

Document 5: Ohashi, T. et al., "Reduction of lysomal storage in murine mucopolysaccharidosis type VII by transplantation of normal and genetically modified macrophages", Blood (2000), Vol. 95, No. 11, pages 3631 to 3633

Document 6: WO 2000/070070 A1 (DNAVEC Research Inc.), 23

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

November 2000, entire document

Document 7: Akihiro Iida et al., "Sendai Virus no Reverse Genetics wo Katsuyo Shita Shinki Idenshi Chiryoyo RNA Vector", Protein, Nucleic Acid and Enzyme (2003), Vol. 48, No. 10, pages 1371 to 1377

The invention set forth in claims 1 to 4 and 8 to 17 lacks novelty and does not involve an inventive step in the light of documents 1 to 3 cited in the international search report.

Document 1 indicates that an interferon gene is introduced using an adenovirus vector into CD34+ producing stem cells obtained from bone marrow, and that such hematopoietic stem cells can be used in the treatment of leukemia and the like.

Document 2 sets forth cells of bone marrow origin which have had an interferon gene introduced therein using an adenovirus vector, and indicates that said cells of bone marrow origin may be used in the adoptive immunotherapy of cancer.

In addition, document 3 indicates that when mesenchymal cells of bone marrow origin into which the IFN-beta gene has been introduced were injected to a mouse having been injected with melanoma cells, the proliferation of melanoma cells at the tumor site was suppressed; and that mesenchymal cells of bone marrow origin into which said gene was introduced can be used in gene delivery during gene therapy of cancer.

Documents 1 to 3 do not indicate that hematopoietic stem cells into which genes have been introduced are used in the treatment of liver disorders, but cells of bone

marrow origin into which genes have been introduced cannot be distinguished from cells per se, therefore there is no discernible different between the invention set forth in claims 1 to 4 and 8 to 17 of this application and the invention set forth in document 1.

The invention set forth in claims 1 to 5 and 8 to 17 lacks novelty and does not involve an inventive step in the light of document 4 cited in the international search report.

Document 4 sets forth mesenchymal stem cells of bone marrow origin having an HGF gene introduced therein using an adenovirus, and gene therapy for ischemic disorders.

The invention set forth in claims 1, 2 and 8 to 16 lacks novelty and does not involve an inventive step in the light of document 5 cited in the international search report. Document 5 indicates that transplanting mesenchymal cells of bone marrow origin having beta-glucuronidase gene introduced therein using a retrovirus vector into a mouse with lysosomal accumulation disorder resulted in an improvement to lysosomal accumulation in the liver and kidneys.

The invention set forth in claims 17 to 19, 25 and 26 does not involve an inventive step in the light of document 5 cited in the international search report.

It would be easy for a person skilled in the art to conceive of producing a therapeutic drug for gene therapy using the transformed hematopoietic stem cells of the invention disclosed in document 5.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The invention set forth in claims 20, 22, 27 and 29 does not involve an inventive step in the light of documents 1 to 3 cited in the international search report.

The mesenchymal stem cells of bone marrow origin of the invention set forth in documents 1 to 3 have an effect on tumours which are not specific to particular tissue or organs, therefore it would not be particularly difficult for a person skilled in the art to attempt to use the aforementioned mesenchymal stem cells of bone marrow origin in gene therapy for hepatic cancer.

The invention set forth in claims 4, 23, 25, 26 and 30 does not involve an inventive step in the light of documents 1 to 5 cited in the international search report.

As disclosed in documents 1 to 4, it is a known technique to use an adenovirus vector as a vector when carrying out gene therapy using cells of bone marrow origin having had genes introduced therein, therefore it would be easy for a person skilled in the art to conceive of using an adenovirus vector as an alternative to a retrovirus vector in the invention set forth in document 5.

The invention set forth in claims 4, 6, 7, 23, 24, 30 and 31 does not involve an inventive step in the light of documents 1 to 7 cited in the international search report.

Document 6 indicates that a GFP gene was introduced into mouse bone marrow cells using a Sendai virus vector.

Document 7 indicates that an F-deficient Sendai

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

virus vector exhibits good gene introduction efficiency in a variety of different cells, and that a Sendai virus vector containing a FGF-2 gene is used in an ischemic disorder model of gene therapy.

The inventions set forth in documents 1 to 6 share the same technical field in pertaining to methods of introducing genes into cells of bone marrow origin with the object of gene therapy. In addition, it is known that an F-deficient recombinant Sendai virus vector exhibits good gene introduction efficiency in a variety of different cells, as disclosed in document 7, therefore it would be easy for a person skilled in the art to conceive of attempting to use a Sendai virus vector as a vector when introducing genes into bone marrow cells, and selecting FGF2 as a loaded gene in the inventions set forth in documents 1 to 5, in the light of documents 6 and 7.

The invention set forth in claims 21 and 28 involves an inventive step in relation to documents cited in the international search report.

In particular, none of the documents indicates or suggests that cells of bone marrow origin having had either the HGF or FGF gene introduced therein are used in gene therapy for liver disorders.